BRIEF COMMUNICATION

Clobazam-treated patients with Lennox-Gastaut syndrome experienced fewer seizure-related injuries than placebo patients during trial OV-1012

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Epilepsia, 57(6):e113–e116, 2016
doi: 10.1111/epi.13388

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Summary

Drop seizures are especially problematic in patients with Lennox-Gastaut syndrome (LGS) because of their potential for serious injury. In this post hoc analysis of phase 3 OV-1012 data, a medical review was conducted of seizure-related injuries based on Medical Dictionary for Regulatory Activities (MedDRA) preferred terms from all adverse event (AE) listings. Patients receiving clobazam experienced fewer seizure-related injuries than those receiving placebo (8.9% all clobazam dosages vs. 27.1% placebo, $p \leq 0.05$). Significant differences in the rates of seizure-related injuries were observed for the medium- and high-dosage clobazam treatment groups (4.8% and 10.2%, respectively, $p \leq 0.05$). A total of 50 of 53 AEs considered seizure-related were mild or moderate in intensity; 3 severe AEs occurred in the placebo group (fall, contusion, and jaw fracture). A single serious AE (jaw fracture, which required hospitalization and surgery) occurred in a placebo-treated patient. Most injuries resolved by the end of the study. This analysis indicates that the reduction in drop-seizure frequency achieved with clobazam provides a clinically meaningful benefit, a reduced likelihood of experiencing seizure-related injuries.

KEY WORDS: **Clobazam, Lennox-Gastaut syndrome, Drop seizure, Injury.**

Lennox-Gastaut syndrome (LGS) is a severe childhood-onset epileptic encephalopathy characterized by electroencephalography (EEG) with slow (≤2.5 Hz) spike-and-waves, several seizure types, and, typically, developmental delays and behavioral disturbances.[1] Onset generally occurs between 3 and 8 years of age, with peak occurrence between 3 and 5 years.[1] Most patients with LGS continue to experience refractory epilepsy and cognitive impairment that persist into adulthood.

Among the seizure types associated with LGS are tonic, atonic, and atypical absence, which often are resistant to antiepileptic medications.[2] Drop seizures (tonic or atonic falls, also known as drop attacks) are especially problematic because they are the most common type, occur suddenly, and have the potential to cause injury.[3] Antiepileptic drugs (AEDs) that reduce seizure frequency—especially drop seizures—are desirable not only to improve seizure control, but also to prevent injuries in patients with LGS.

In October 2011, clobazam (ONFI) received U.S. Food and Drug Administration (FDA) approval for the adjunctive treatment of seizures associated with LGS in patients 2 years and older based on efficacy in reducing seizure frequency. In phase 3 study OV-1012,[4] three clobazam dosages (0.25, 0.5, and 1.0 mg/kg/day [low-, medium-, and high-dosage, respectively]) were evaluated. Average weekly reductions in drop-seizure rates with clobazam treatment were significantly greater than with placebo: 12% for placebo versus 41%, 49%, and 68% for clobazam low-, medium-, and high-dosage groups, respectively (all $p < 0.05$). Significant differences versus placebo in ≥50% responder rates were observed for medium- and high-dosage clobazam groups (59% and 78%, respectively, vs. 32%; $p < 0.05$).

Accepted March 21, 2016; Early View publication May 4, 2016.
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The standard end points used in clinical trials to evaluate an active drug against placebo are useful in demonstrating efficacy, but it is often unclear whether these measures are clinically meaningful. For example, although statistically significant differences from placebo were observed in drop-seizure frequency with adjunctive clobazam in patients with LGS in study OV-1012, whether this translated to decreased medical morbidity is unknown. We evaluated the rates of seizure-related injuries in patients receiving different clobazam dosages versus placebo to determine its impact on injuries related to drop seizures. This is a novel approach to assessing efficacy of a new treatment, by evaluating its impact on a relevant nonseizure clinical outcome. The results of this post hoc analysis are presented herein.

Methods

Data for this post hoc analysis of seizure-related injuries were obtained from trial OV-1012 (NCT00518713).[4] Because the trial methodology and outcomes have been published previously, the study design is briefly summarized below.

Study design

OV-1012 was a phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group study conducted in patients 2–60 years of age with a diagnosis of LGS. Patients eligible for participation were required to have documented LGS onset by 11 years of age, were receiving stable dosages of 1–3 AEDs (except benzodiazepines) for ≥30 days, and were experiencing ≥2 drop seizures per week. The study included a 4-week baseline period, a 3-week titration period, and a 12-week maintenance period.

During the baseline period, patients were stratified by weight (12.5–≤30 and >30 kg) prior to randomization to placebo or one of three clobazam treatment groups: low dosage (target of 0.25 mg/kg/day [maximum 10 mg/day]), medium dosage (target of 0.5 mg/kg/day [maximum 20 mg/day]), and high dosage (target of 1.0 mg/kg/day [maximum 40 mg/day]). The primary efficacy end point was percentage decrease in mean weekly drop seizure rates during maintenance versus baseline phases for the modified intention-to-treat (mITT) population; secondary outcomes included other seizure types and responder rates. Routine safety assessments were performed.

Post hoc assessment of seizure-related injuries

For this post hoc analysis, medical review of all adverse event (AE) listings, based on Medical Dictionary for Regulatory Activities (MedDRA) preferred terms (Version 12.0),[5] in OV-1012 was conducted to identify AE terms considered to be consistent with seizure-related injuries. Injuries not related to seizures were also captured. Medical reviews were conducted independently by one pediatric neurologist (D. Lee), one adult neurologist (J. Isojarvi), and confirmed by an independent adult neurologist (V. Shen, see Acknowledgments).

AEs occurring after receiving study drug through 30 days after the last dose of study medication were summarized by intensity (mild, moderate, or severe) as well as by relationship to treatment (not related, possibly related, or probably related) and by seriousness.

Statistical analyses

The safety population included all randomized patients who received ≥1 dose of study drug. Descriptive statistics are provided. Fisher's exact test was used for statistical comparison between treatments in the number of seizure-related injuries.

Results

Patient disposition

Of 301 patients screened, 238 were randomized at 51 sites in the United States (165 patients at 33 sites), India (55 patients at 13 sites), and Europe/Australia (18 patients at five sites). A total of 217 patients comprised the mITT population, and 177 completed the study.

Seizure-related injuries

Patients receiving clobazam experienced significantly fewer seizure-related injuries than those receiving placebo ($p < 0.05$) (Fig. 1). Compared with placebo (27.1%), the rates of seizure-related injuries were statistically

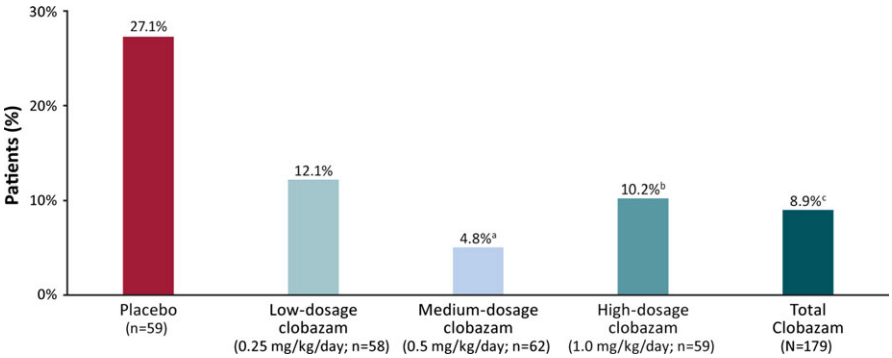

Figure 1.
Patients experiencing seizure-related injuries during phase 3 trial OV-1012 by treatment group (safety populations). [a]$p < 0.001$ versus placebo; [b]$p < 0.03$ versus placebo; [c]$p \leq 0.05$ versus placebo.
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Table 1. Patients experiencing seizure-related injuries during phase 3 trial OV-1012

		Clobazam dosage		
	Placebo (n = 59)	Low 0.25 mg/kg/day (n = 58)	Medium 0.5 mg/kg/day (n = 62)	High 1.0 mg/kg/day (n = 59)
n (%)	16 (27.1)	7 (12.1)	3 (4.8)[a]	6 (10.2)[b]
Events by preferred terms (no. of events in group)				
	• Excoriation (5) • Skin laceration (4) • Contusion (3) • Falls (3) • Head injury (2) • Local swelling (2) • Concussion • Conjunctival hemorrhage • Face injury • Foot fracture • Hematoma • Jaw fracture • Joint sprain • Periorbital hematoma • Thermal burn	• Contusion (2) • Head injury (2) • Face injury • Greenstick fracture • Mouth injury • Periorbital infection • Skin laceration • Upper limb fracture • Wound infection	• Contusion (2) • Excoriation • Fall	• Excoriation (3) • Contusion (2) • Skin laceration (2) • Clavicle fracture • Lower limb fracture • Tooth fracture

[a] $p < 0.001$ versus placebo.
[b] $p < 0.03$ versus placebo.

significantly lower for the medium- (4.8%, $p < 0.001$) and high-dosage (10.2%, $p < 0.03$) clobazam groups, but not for the low-dosage clobazam group (12.1%).

A total of 32 patients experienced 53 AEs that were considered to be seizure-related (Table 1), of which 50 (94.3%) were mild or moderate in intensity. All severe seizure-related AEs occurred in the placebo group, with three patients experiencing one severe AE each (fall, contusion, or jaw fracture). In all treatment groups, all but one of the injuries were not serious, and most resolved by study end. The single serious AE (jaw fracture, which required surgery) occurred in a placebo-treated patient; this was the only seizure-related injury that required hospitalization.

Only one patient in the high-dosage clobazam group experienced a non–seizure-related injury (scratch, mild intensity).

Discussion

In this post hoc analysis of study OV-1012, the frequency of seizure-related injuries was significantly lower for clobazam-treated patients than for those treated with placebo. This observation is consistent with what is known about drop seizures—they usually cause falls and injury. This analysis suggests that the reduction in drop-seizure frequency achieved with clobazam treatment[4] provides a clinically meaningful benefit by reducing the likelihood of seizure-related injuries; there was only one non–seizure-related injury, and therefore no evidence to suggest that the drug was associated with injuries. The analysis also helps to validate the clinical utility of the drug; however, the analysis has limitations (discussed below).

For most randomized clinical trials in epilepsy, an AED is considered efficacious when treatment achieves a statistically significant difference from placebo in median seizure-frequency reduction from baseline and/or responder rate (≥50% reduction in seizure frequency from baseline). These efficacy measures provide valid, reproducible data from a reasonable sample size[6]; however, simply counting seizures may not be as clinically meaningful as evaluating the consequences that such trial end points have on patients' lives (e.g., injury rates, driving status, employment status, overall healthcare costs, and death—including sudden unexpected death in epilepsy [SUDEP]). For example, in a meta-analysis by Ryvlin et al.,[7] patients with uncontrolled epilepsy who received adjunctive AEDs not only experienced a reduction in seizure frequency, but were as much as one-seventh as likely to experience SUDEP than those who received placebo. In that meta-analysis, the reduced rate of SUDEP can be considered a clinically extremely important marker for efficacy of adjunctive AED therapy. Likewise, the reduction in seizure-related injuries in clobazam-treated patients with LGS represents a clinically meaningful treatment outcome beyond the primary trial end point. Because the type of data used in this analysis is routinely collected in clinical trials, it is possible to show a clinically meaningful difference between the active drug and placebo with currently used study designs and methodology. Furthermore, these results help validate the value of FDA criteria for approval, and perhaps these types of markers are more valuable than measuring seizure reduction when assessing drug

efficacy. These designs and methods might, however, require modification depending on the seizure types and epilepsy syndromes studied.

These preliminary findings are of clinical interest; however, this post hoc analysis must be interpreted with caution. A notable limitation is that the seizure-related injury terms were not specified prospectively and were determined on a case-by-case basis. Age is another factor that could be explored in order to unequivocally attribute the decrease in seizure-related injuries to the reduction in drop-seizure frequency with clobazam treatment. Furthermore, the incidence of the preferred term "falls" may be underrepresented because standard AE coding practice did not distinguish seizure-related injuries resulting from falls from those that were not. Finally, patients' degree of disability affects their chances of sustaining a seizure-related injury from drop seizures. For example, patients able to walk freely are more likely to sustain injury from fewer drop seizures than those who are wheelchair bound and experience a greater number of drop seizures.

In conclusion, for patients with LGS, this post hoc analysis suggests that typical trial end points combined with an evaluation of seizure-related injuries may provide a better understanding of the overall effectiveness of AEDs in improving patients' clinical outcomes. Linking the primary trial end point of seizure reduction with a real-world measure of morbidity offers some validation of that seizure outcome end point, and also suggests that it may be possible to design some trials with more meaningful and clinically relevant end points.

Acknowledgments

This analysis (support) was funded by Lundbeck LLC. The authors would like to thank Dr. Vivienne Shen, MD, PhD, Lundbeck LLC (Deerfield, IL) for her independent review of the injury data. Dr. Deborah Lee, MD, PhD, was an employee of Lundbeck LLC when the analysis was conducted. Editorial support, including incorporating author comments, preparing tables and figures, and coordinating submission requirements, was provided by Apurva Davé, PhD, of Prescott Medical Communications Group (Chicago, IL).

Disclosure of Conflict of Interest

Dr. Isojarvi and Mr. Peng are employees of Lundbeck LLC. Dr. Lee was an employee of Lundbeck LLC, at the time the study was conducted. Dr. Sperling has received grants (to Thomas Jefferson University) from the National Institute of Neurological Disorders and Stroke (NINDS), Defense Advance Projects Research Agency (DARPA), UCB Pharma, Sunovion Pharmaceuticals Inc., Eisai, SK Life Sciences, Upsher-Smith, Medtronics, Lundbeck, Accorda, GlaxoSmithKline, Pfizer, and Brain Sentinel. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

References

1. Arzimanoglou A, French J, Blume WT, et al. Lennox-Gastaut syndrome: a consensus approach on diagnosis, assessment, management, and trial methodology. *Lancet Neurol* 2009;8:82–93.
2. Michoulas A, Farrell K. Medical management of Lennox-Gastaut syndrome. *CNS Drugs* 2010;24:363–374.
3. Camfield PR. Definition and natural history of Lennox-Gastaut syndrome. *Epilepsia* 2011;52(Suppl. 5):3–9.
4. Ng YT, Conry JA, Drummond R, et al. Randomized, phase III study results of clobazam in Lennox-Gastaut syndrome. *Neurology* 2011;77:1473–1481.
5. Medical Dictionary for Regulatory Activities. Available at: http://www.meddra.org/. Accessed March 11, 2016.
6. Gilliam F. What we don't learn from clinical trials in epilepsy. *Epilepsia* 2003;44(Suppl. 7):51–54.
7. Ryvlin P, Cucherat M, Rheims S. Risk of sudden unexpected death in epilepsy in patients given adjunctive antiepileptic treatment for refractory seizures: a meta-analysis of placebo-controlled randomised trials. *Lancet Neurol* 2011;10:961–968.